UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/579,294	05/02/2007	Ryo Sudo	09707.0011	6583

22852 7590 03/08/2010

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER LLP
901 NEW YORK AVENUE, NW
WASHINGTON, DC 20001-4413

EXAMINER	
NGUYEN, QUANG	
ART UNIT	PAPER NUMBER
1633	

MAIL DATE	DELIVERY MODE
03/08/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/579,294	SUDO ET AL.	
	Examiner	Art Unit	
	QUANG NGUYEN, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 December 2009 and 23 November 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/03/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment filed on 11/23/09 was entered.

Amended claims 1-14 are pending in the present application.

Information Disclosure Statement

All cited documents in the IDS filed on 12/3/09 were considered by **the examiner who has no knowledge in Japanese**. However, the notification of reasons for rejection dated December 2, 2008 was crossed through because it does not conform to 37 CFR 1.98 (a)(3) b(5); and it is not in a suitable form to be printed on the face of an issued US patent. With respect to Japanese documents submitted in this IDS as well as those in the IDS filed on 5/15/06 and without English translation, **once again please note that the examiner has absolutely no knowledge in Japanese**.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Amended claims 1-2, 6-7 and 11-14 are rejected under 35 U.S.C. 102(b) as being anticipated by Yamato et al (WO 02/10349; IDS) (See US 2004/0028657 for the English version) and evidenced by Shimizu et al (Biomatrials 24:2309-2316, 2003; IDS).

This is a new ground of rejection necessitated by Applicant's amendment with the new limitation "a three-dimensional tissue with a permeable sheet".

Yamato et al already disclose at least a method for producing a multi-layered cultured skin sheet, said method comprising the steps of: (a) culturing epidermal cells (e.g., keratinocytes, melanocytes) on a cell culture support having a substrate surface coated with a temperature-responsive polymer whose lower critical solution temperature in water is 0-80^{0}C; (b) bringing the temperature of the culture solution to below the lower critical solution temperature; (c) bringing the cultured epidermal sheet into close contact with a polymer membrane; (d) peeling the adhering sheet off together with the polymer membrane; and (e) allowing the epidermal cultured cell sheet in close contact with the polymer membrane of step (d) to adhere to a cell culture support coated with a temperature-responsive polymer; and the polymer membrane in close contact is thereafter peeled off to form multiple culture cell layers **OR** the cellular sheet in intimate contact with the polymer membrane is turned over and fixed on the cell culture support such that the polymer membrane contacts the support; another cellular sheet is allowed to adhere to the first cellular sheet; and thereafter, a medium is added to peel off the polymer membrane from the second cellular sheet, to which yet another cellular sheet is allowed to adhere and the process is repeated to form a multiple of cellular sheets (see at least paragraphs 15-19, 29, 38-42 and claims 4-5). Yamato et al also disclosed exemplified temperature-sensitive polymers include homopolymers or co-polymers of (meth)acrylamide compounds, N-(or N,N-dialky-substituted (meth)acrylamide derivatives (e.g., polyisopropylacrylamide or PIPAAm), vinyl ether derivatives

(paragraphs 33, 67, 82); and exemplified polymer membranes include PVDF, polyethylene, cellulose, chitin, chitosan, collagen, polyurethane membranes (paragraph 37). Yamato et al further disclose that the multilayered cultured skin sheet are adapted for use in the treatment of a burn or a wound that are gouged deep into a skin tissue in a living body, including a nude rat (paragraphs 20-21, 42, 45 and example 82). Yamato et al stated "The sheets of the invention are also characterized in that the cell-to-substrate protein resembling the basal lamina that was formed during the culture has not been destroyed enzymatically" (middle of paragraph 30); and "In particular, the multi-layered cultured skin sheet of the invention is distinct from the conventional cultured skin sheets in that it keeps the basal membrane protein intact; hence when it is used as a skin graft, it will adhere viably to the tissue of the diseased part even if it is gouged deep" (middle of paragraph 45).

Please note that at least the above disclosed polymer membranes are permeable sheets and/or each of the basal lamina (extracellular matrix layer) underneath each epidermal cultured cell sheet formed during the culture would also constitute as a distinct permeable sheet as evidenced at least by the teachings of Shimizu et al using the same cell sheet engineering approach with PIPAAm-grafted surfaces (see at least Figures 2 and 3). Therefore, a multilayered cultured skin sheet that is taught by Yamato et al., falls within the breadth of a three-dimensional tissue or an artificial organ as claimed. With respect to claims 12-13, by disclosing the use of various polymer membranes such as include PVDF, polyethylene, cellulose, chitin, chitosan, collagen, polyurethane membranes to achieve close contact with the epidermal cell sheet or the

multilayered skin sheet, it is a means of defining a colony form of the cultured cells by controlling a position of a pore in a permeable sheet because these various polymer membranes or sheets have different pore positions/sizes.

Accordingly, the teachings of Yamato et al meet the limitations of the instant claims as broadly written. Therefore, the reference anticipates the instant claims.

Response to Arguments

Applicants' arguments related in part to the above rejection in the Amendment filed on 12/03/09 (pages 4-7) have been fully considered but they are respectfully not found persuasive for the reasons discussed below.

Applicants argue basically that the Yamato reference can not anticipate the instant claims because the reference teaches that the polymer membrane as a temporary support for the skin cells as a way to improve the process of peeling off the cell culture from the culture support; and also after the cell culture is peeled off of the culture support, the polymer membrane is peeled away as well. In contrast, the permeable sheet remains in contact with the cultured cells such that a "three-dimensional tissue with a permeable sheet" results. With respect to claims 12-13, Applicants argue that the limited time of contact between the polymer membrane and the cells is not long enough for the cells to grow on the polymer membrane and be influenced by the pore structure of the polymer membrane; and that the Yamato reference teaches that the cell culture grows and forms on the culture support and not

on the polymer membrane. Therefore, the polymer membrane would not influence how colonies of cells form as they grow in culture.

First, during various exemplified preparation processes, a laminated cultured skin sheet of Yamato et al always contains a polymer membrane (see at least paragraphs 39, 41 and claims 4-10) and that eventually the polymer membrane is peeled off. It should be noted that the polymer membrane could also be peeled off after transplantation into a living body (see paragraph 42). The laminated cultured skin sheet of Yamato et al prior to the eventual peeling off the polymer membrane is indistinguishable from a three-dimensional tissue with a permeable sheet as claimed.

Second, please also note that each of the basal lamina (extracellular matrix layer) underneath each epidermal cultured cell sheet formed during the culture would also constitute as a distinct permeable sheet as evidenced at least by the teachings of Shimizu et al using the same cell sheet engineering approach with PIPAAm-grafted surfaces as discussed in the above rejection.

Third, claim 12 simply recites "defining a colony form of the cultured cells by controlling a position of a pore in said permeable sheet". There is no requirement whatsoever any culture time period. Paragraph 40 in the Yamato reference indicates clearly that the cellular sheet in intimate contact with the polymer membrane must be under a culture condition for a significant period of time to form a multiple of cellular sheets one on top of another. Additionally, please also note that paragraph 39 of the Yamato reference which indicates that the cellular sheet in intimate contact with the

polymer membrane is allowed to adhere to the cell culture support, is only one of several specific embodiments or examples.

Claims 1-3, 6-8 and 11 are rejected under 35 U.S.C. 102(b) as being anticipated by Yamato et al. (Material Integration 13:58-64, 2000 and its English translation; IDS). ***This is a new ground of rejection based on an information disclosure statement under 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p) on 12/03/09.***

Yamato et al teach a three-dimensional co-culture comprising combining, layering and overlaying cell sheets, including the stable layered structure comprising hepatocyte sheets and non-parenchymal cell sheets (an artificial organ), that have been recovered without damaging any functions, from temperature-responsive intelligent culture dishes (see at least the section entitled "5 Three-dimensional co-culture, particularly the last 3 lines on page 11 continue to page 12; and Figure 6 in the translated document). Yamato et al also teach that each cell sheet that has been recovered from temperature-responsive culture dishes contains an extracellular matrix (ECM) layer formed during the culture underneath the cell monolayer and attached to the cell monolayer via ECM receptors expressed on the surface of the cell membrane (page 8; Figure 4). Accordingly, each distinct ECM layer underneath each hepatocyte/non-parenchymal cell sheet formed during the culture would constitute as a distinct permeable sheet. Therefore, the three dimensional co-culture method of Yamato et al contains the same method step and starting materials as those in the method as broadly claimed, and the resulting stable layered structure comprising

hepatocyte sheets and non-parenchymal cell sheets of Yamato et al is indistinguishable from the compositions as broadly claimed.

Therefore, the reference anticipates the instant claims as written.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Amended claims 1-10 are still rejected under 35 U.S.C. 103(a) as being unpatentable over Mitaka et al (WO 02/088332; IDS; see US 2004/0073391 for the English version) in view of Germain et al (US 7,521,231) for the same reasons already set forth in the Office action mailed on 8/21/09 (pages 7-9). ***The same rejection is restated below.***

Mitaka et al disclose at least a method for inducing a liver tissue from small hepatocyte colonies by placing the small hepatocyte-rich colonies onto a sheet of a biocompatible material which is bioabsorbable or biodegradable, and further culturing them for a given period of time (see at least summary of the invention, particularly paragraphs 24, 67-72). Mitaka et al also teach that the biocompatible and bioabsorbable sheets to be used include collagen sheets, collagen sponges, polyglycolic acid sheets (paragraph 69), and the liver tissue thus formed on the sheet can be used for transplantation of the liver as a whole without separating the sheet (paragraph 72). In an exemplification, Mitaka et al observed the formation of bile canaliculi by small hepatocytes seeded on a collagen sheet or a polyglycolic acid felt sheet (example 4).

Mitaka et al do not teach specifically a three-dimensional cell culture method comprising constructing a three-dimensional tissue by stacking cells, including small hepatocytes, flat-cultured on a permeable sheet on other flat-cultured cells together with the permeable sheet; and the same three-dimensional tissue construct.

At the effective filing date of the present application, Germain et al already taught a method for preparing a human or animal tissue by applying a compressive force to a stack of sheets of living tissue thereby inducing adjacent layers to fuse or adhere to each other with each sheet of living tissue is comprised of cells and an endogenous extracellular matrix; and the resulting multi-layer tissue construct (thickness of between about 0.01 mm to about 0.5 mm) may comprise between two and twelve sheets of living tissue and the sheets may be of different types (see at least the abstract and Summary

of the Invention; col. 3, lines 21-44). Germain et al also teach that multi-layer tissue constructs are thicker and therefore stronger and since multi-layer tissue constructs can comprise more than one sheet of living tissue, they can be designed to more closely resemble the tissues that they intended to replace (col. 1, lines 47-51). Germain et al also disclose that the method utilized cells cultured in vitro as a sheet of living tissue, and utilized cells include adult stem cells, hepatocytes, parenchymal cells and others (col. 3, lines 6-20).

Accordingly, it would have been obvious for an ordinary skilled artisan to modify the teachings of Mitaka et al by also forming a multi-layer liver tissue construct by applying a compressive force to a stack of sheets made of a biocompatible material (e.g., collagen sheets or polyglycolic acid sheets) already seeded with cultured small hepatocyte-rich colonies in light of the teachings of Germain et al as discussed above.

An ordinary skilled artisan would have been motivated to carry out the above modification because Germain et al already teach that multi-layer tissue constructs are thicker and therefore stronger and since multi-layer tissue constructs can comprise more than one sheet of living tissue, they can be designed to more closely resemble the tissues that they intended to replace.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Mitaka et al and Germain et al., coupled with a high level of skill for an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

Applicants' arguments related in part to the above rejection in the Amendment filed on 12/03/09 (pages 7-9) have been fully considered but they are respectfully not found persuasive for the reasons discussed below.

Applicants argue basically that the teachings of Mitaka and Germain references in combination are not compatible. This is because Germain's sheets of cells do not include exogenous materials such as a biocompatible sheet or a substrate akin to Mitaka's biocompatible material and since in Germain's words, it is "essential" to fuse adjacent layers of cell tissue together, one of ordinary skill in the art would not have combined the teachings of Mitaka and Germain because the biocompatible sheets that Mitaka's cells grew on would have prevented the fusion of adjacent layers of cells via Germain's methods.

First, please note that the above rejection is made under 35 U.S.C. 103(a) and therefore none of the cited references has to teach every limitation of the claims. Additionally, it is also improper to consider each of the cited references in total isolation one from the other.

Second, Mitaka et al already teach that the biocompatible and bioabsorbable sheets to be used include collagen sheets; and collagen is one of a major extracellular matrix components and it is present in a living tissue sheet taught by Germain et al. There is no rationale or scientific reasons of record why collagen sheets can not be fused together while living tissue sheets can. Moreover, Mitaka et al teach that the

small hepatocyte-rich colonies penetrate into the cavities in the fiber structure of the sheet and therefore, the concentration of the extracellular matrix secreted by themselves in the narrow cavities is increased to significantly stimulate the maturation (paragraph 68).

Third, please refer to the motivations already set forth in the above rejection why an ordinary skill artisan would have combined the teachings of Mitaka et al and Germain et al.

Conclusion

No claim is allowed.

Applicant's submission of an information disclosure statement under 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p) on 12/03/09 prompted the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 609.04(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's SPE, Joseph T. Woitach, Ph.D., may be reached at (571) 272-0739.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

/QUANG NGUYEN/

Primary Examiner, Art Unit 1633